added claims. Support for the new claims is found in the original claims and in the specification on page 6, lines 15-29. No new matter is added by way of the amendments.

Attached is a marked-up version showing the changes made to the claims by the amendments. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE." In addition, an Appendix of Pending Claims is attached for the Examiner's convenience.

Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow.

Rejection Under 35 U.S.C. §112, first paragraph: written description.

Claims 1-14 and 16-22 stand rejected under 35 U.S.C. §112, first paragraph for lack of sufficient written description. Applicants respectfully traverse.

The Examiner states that only the described HO-I and variants having at least about 80% nucleic acid identity satisfies the written description requirement under 35 U.S.C. § 112, first paragraph. Consistent with the Examiner's rejection, Applicants have cancelled claims 1-3, 13-15, and 26-27 and added claims directed to methods of extending the survival of an organ transplant by contacting the organ transplant cells with a nucleic acid comprising at least about 80% sequence identity to nucleotides 81-944 of SEQ ID NO: 1. Applicants submit that the claims as amended clearly satisfy the written description requirement of § 112, first paragraph as interpreted by the Examiner. Accordingly, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §112, first paragraph: enablement

Claims 1-22 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Specifically, the Examiner concludes that the specification is not enabled for extending survival of an organ transplant by contacting a cell *in vivo* with a nucleic acid encoding heme-oxygenase I or any nucleic acid that "modulates heme oxygenase I." Applicants respectfully traverse.

Applicants have amended the claims to recite use of a nucleic acid with at least about 80% sequence identity to nucleotides 81-944 of SEQ ID NO: 1. The Examiner has indicated that the specification enables extending survival of an organ transplant by *ex vivo* perfusion of the organ prior to transplant with an adenoviral vector encoding heme oxygenase I (HO-I) or variants having at least about 80% sequence identity to nucleotides 81-944 of SEQ ID NO:

1. Consequently, the issues of enablement raised by the Examiner appear to narrow down to whether the bounds of the claimed method is commensurate with the scope of enablement for *(a)* nucleic acid delivery methods other than adenoviral vectors, *(b)* extending graft survival by *in vivo* use, and *(c)* extending graft survival by contacting the organ with the nucleic acid during a period other than prior to transplantation.

The rationale the Examiner appears to advance in support of nonenablement for nucleic acid delivery other than via adenoviral vectors is the lack of a teaching sufficient to overcome the supposed difficulties of delivering the described nucleic acid to achieve the purposes of the claimed method. In particular, the arguments focus on the difficulty of obtaining long term stable gene expression for effective gene therapy, differences in efficiency of nucleic acid delivery into cells (e.g., differences in host range of virus based vectors), and difficulties of systemic administration and targeting of the nucleic acid.

Applicants address these concerns by first noting that long-term stable expression in the manner suggested by the Examiner is not necessary for extending the survival of an organ transplant. For example, Example 1 and Example 3 of the present application disclose that a single exposure to metalloprotoporhyrin in an amount resulting in elevated heme oxygenase-I levels extends survival of the transplanted organ. Similarly, Example 3 demonstrates that a single administration of adenoviral vector encoding human heme oxygenase-I (Ad HO-I) *24 hr before transplant* extended graft survival similar to the administration of metalloprotoporphyrin. Thus, even a short exposure to recombinant viral vector Ad-HO-1 and subsequent transient expression extends survival of the transplanted organ. Notably, the Examiner appears to agree that the claims are enabled for adenoviral vectors despite a later conflicting statement that adenoviral vectors appear unsuitable to achieve the purposes desired because of their immunogenicity and episomal maintenance.

By emphasizing the need for long term stable expression, the Examiner also appears to construe the claims as requiring long term organ survival. However, long term survival of the scope proposed by the Examiner, though desirable, is not a prerequisite to practice the claimed method. In this regard, Applicants invite the Examiner to review the decision of the Federal Circuit in In re Cortright, 49 USPQ2d 1465 (Fed. Cir. 1999). In that case, the claims were directed to a process for restoring hair growth. The Board of Patent Appeals rejected the claims as nonenabling because the disclosed treatment failed to return the user's hair to its original state. The Federal Circuit, however, held that

> Although the PTO must give claims their broadest reasonable interpretation, this interpretation must be consistent with the one those skilled in the art would reach.

See id. at 1467. The court noted that the examples in the specification described individuals who had increased hair growth but did not cure baldness. In view of the disclosure, the court reversed the Board's decision and held that a person skilled in the art would construe the phrase as meaning "increasing the amount of hair grown" on the scalp but not necessarily a full head of hair. The court further indicated that the PTO's and the Board's interpretation conflicted with the meaning given to identical phrases of patents from analogous art:

> Accordingly, the PTO's interpretation of claim terms should not be so broad that it conflicts with the meaning given to identical terms in other patents from analogous art.

See id. at 1407.

Similarly, the present claims are directed to extending survival of an organ transplant in the manner disclosed. This interpretation is consistent with patents issued by the PTO containing claims with the phrase "extending survival of an organ transplant," such as in Exhibit A, U.S. Patent No. 5,756,492 and Exhibit B, U.S. Patent No. 6,013,641, which disclose methods for extending graft survival for similar time periods as described in the present application. Similar support is found in the references discussed below, for example Exhibit E (see Figure 2), Exhibit I, (see Figure 2), and Exhibit L, (see Figure 6).

Moreover, benefits of the claimed method are not limited to long term organ survival (specification on page 26, lines 17-19):

> This can be useful in areas where xenogeneic grafts have been used awaiting an allogeneic graft, to allow for reduced amount of immunosuppressants or avoid using immunosuppressants altogether.

Additional advantages arise from protection of an organ against cold ischemia/reperfusion (I/R) injury, a significant factor in determining organ integrity during organ storage and subsequent transplant (specification, page 37, lines 4-12):

> The beneficial effects in the ex-vivo I/R injury model were reflected by the ability of exogenously upregulated HO-1 to improve portal vein blood flow, increase bile production, and depress sGOT levels, all accepted parameters of hepatic function. Portal blood flow is mostly affected by resistance in the graft caused by lobular ballooning, hepatocyte swelling, and sinusoidal congestion. In this ex vivo perfusion model, the improved portal venous blood flow represents less hepatocyte

> injury and lobular disarray in the liver rather than the endothelium-dependent vasodilatory effects of carbon monoxide. Collectively, these results are consistent with the ability of HO-1 to protect cells from oxidative injury.

Hence, a person knowledgeable in the art in view of the present disclosure would have reached a different conclusion than one advanced in the Office Action.

Another concern discussed by the Examiner is the variability in efficiency of introducing DNA into cells by viral or non-viral techniques. These include variable host range of viral vector systems, differences in their ability to infect dividing and non-dividing cells, and inefficiency of non-viral delivery methods, for instance liposomes and naked DNA. This reasoning, however, contrasts with what was known in the art at the time of filing of this application. Applicants invite the Examiner to review the following articles pertaining to delivery of genes into organs and tissues for gene therapy:

(1) Exhibit C: Kuemmerle, N.B. et al., "Gene expression after intrarenal injection of plasmid DNA in the rat," *Pediatr. Nephrol.* 14(2):152-157 (2000), describes intravenous administration or injection of naked DNA into the cortical region of rat kidney and sustained reporter gene expression for at least 8 days and detectable presence of reporter protein for up to 6 months;

(2) Exhibit D: Song, Y.K. et al., "Enhanced gene expression in mouse lung by prolonging the retention time of intravenously injected plasmid DNA," *Gene Ther.* 5(11):1531-1537 (1998), describes transfection of lung by intravenous administration and subsequent expression of luciferase reporter gene; prior administration of cationic lipids increases efficiency of naked DNA uptake and reporter gene expression;

(2) Exhibit E: Qin, L et al., "Multiple vectors effectively achieve gene transfer in a murine cardiac transplant model," *Transplantation* 59:809-816 (1995), describes direct injection into heart allografts of naked DNA vector encoding TGF-β1 to significantly prolong graft survival; the study further illustrates that even low level transient expression of the indicated gene extended graft survival in this transplant model;

(2) Exhibit F: Bueler, H., "Adeno-associated viral vectors for gene transfer and gene therapy," *Biol. Chem.* 380(6):613-622 (1999), describes long term *in vivo* expression using adenoassociated vectors (rAAV), including genes larger than human HO-I (insert capacity of the viral vector is approximately 4.5 kb) without adverse immune response or toxicity; the article states that "one of the most attractive features of rAAV is their low or lacking immunogenicity." (see page 617, right column);

(3) Exhibit G: Xia Q.I. et al., "Production of High Titre Recombinant Adeno-Associated Virus Vectors in the Absence of Helper Adenovirus," *J. Virol.* 72:2224-2232 (1998), explains that use of helper viruses is for *preparing viruses* rather than for direct therapeutic application as suggested in the Office Action; in addition, availability of packaging cell lines eliminates the need of helper viruses;

(3) Exhibit H: Marconi, P. et al., Replication-defective herpes simplex virus vectors for gene therapy in vivo," *Proc. Natl. Acad. Sci. USA* 93:11319-11320 (1996), describes use of herpes virus to express reporter genes up to 4 weeks *in vivo* (page 11320, left column);

(5) Exhibit I: Qin, L. et al., "Retrovirus-mediated transfer of viral IL-10 gene prolongs murine cardiac allograft survival," *J. Immunol.* 156:2316-2323 (1996), describes delivery of recombinant retroviruses encoding IL-2 into cardiac allografts to extend organ survival;

(6) Exhibit J: Shaked, A. et al., "Retroviral-mediated gene transfer into rat experimental liver transplant," *Transplantation* 57: 32-34 (1994), describes use of retroviral vectors to express exogenous genes in liver grafts, thus supporting use of retroviral vectors for delivery of genes into different organs;

(7) Exhibit K: Boasquevisque, C.H. et al., Liposome-mediated gene transfer to lung isografts," *J. Thorac. Cardiovasc. Surg.* 114:783-791 (1997), describes *in vivo* and *ex vivo* delivery of chloroamphenicol transferase reporter gene into lung isografts via liposomes;

(7) Exhibit L: Li, X.K., "Prolonged survival of rat liver allografts transfected with Fas ligand-expressing plasmid," *Transplantation* 66:1416-1423 (1998), shows use of hemagglutin tagged liposomes to deliver FasL gene *in vivo* to extend survival of liver allografts;

(8) Exhibit M: Arhehali, A. et al., "Direct gene transfer into donor hearts at the time of harvest," *J. Thoracic Cardiovasc. Surg.* 109(4):716-719 (1995), describes delivery into donor hearts of DNA encapsulated in cationic liposomes; expression of reporter gene is observed in regions important in immune response in the transplanted heart.

In addition, Exhibit 6 (Lee, R. L. et al., "Isolated Lung Liposome-Mediated Gene Teranfer Produces Organ Specific Transgenic Expression," *Ann. Thorac. Surg.* 66:903-907 (1998)) submitted in Applicants' prior response of October 1, 2001 describes *in vivo* administration of liposome encapsulated DNA and subsequent strong expression of reporter gene in heart and lung (see Abstract). These references provide ample evidence that various methods (e.g., viral vectors, liposomes, and naked DNA) for delivering genes into target organs, particularly for extending graft survival, were known and used at the time of filing of the instant application. As held by the Federal Circuit,

> The specification need not disclose what is well known to those skilled in the art and preferably omits that which is well known to those skilled and already available to the public

See In re Buchner, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); see also M.P.E.P.§ 2164.05. Moreover, M.P.E.P. § 2164.08 following the decisions of the Federal Circuit provides

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with no more effort than is normally required in the art.

In view of the disclosure and the submitted references, a person skilled in the art at the time of filing had sufficient knowledge and experience to choose an appropriate nucleic acid delivery system to practice the claimed subject matter and achieve the desired results without undue experimentation.

The second issue raised by the Examiner for nonenablement is the lack of examples showing extension of graft survival by *in vivo* administration. Applicants invite the Examiner to review Example 3 of the specification showing extension of graft survival by treatment with Ad vectors encoding HO-I. The donor animals were *treated with Ad-HO-I intravenously 24 hrs before harvest* (page 30, lines 2-3). In other words, the viral particles were introduced *in vivo* into the animal before harvesting the organ. The harvested livers were then stored at 4°C before being transplanted into recipients. Consequently, Applicants have reduced to practice *in vivo* delivery of the nucleic acid and subsequent extension of graft survival. In addition, the references discussed above disclose numerous instances of efficient *in vivo* expression of exogenous genes, including for purposes of extending viability of transplanted organs.

The Examiner additionally cites lack of specific tissue targeting and variable transfer efficiency *in vivo* as supporting nonenablement. Any analysis of enablement, however, must not disregard the teachings of the specification. In this case, the examples show that intravenous administration (i.e., *in vivo*) of Ad-HO-I vector extends survival of a transplanted organ, even in the absence of specific targeting. Tissue or cell targeting is not necessary to achieved the desired results. This conclusion is further supported by the exhibits above where delivery of nucleic acids to target cells or organs without tissue targeting mechanisms was effective in expressing an exogenous gene product in the subject organs. In addition, the reference of Miller et al., *FASEB J.* 9:190-199 (1995) cited by the Examiner shows that the skilled artisan knew of particular delivery methods (i.e., localized delivery) to enhance targeting to organs or cells. This reference is in concert with the description in the specification (page 25, lines 13-14 and 18-19):

> In a preferred embodiment, the nucleic acid is contacted with cells of a organ transplant by direct injection into the transplanted organ. . . . In a preferred emdodiment, the nucleic acid is contacted with the cells of a transplant organ by intravascular injection proximate to the transplant organ.

Although it is desirable to enhance therapeutic results by specific targeting to an organ or cell type, enhanced efficacy is an improper standard for determining enablement in this instance.

The third issue raised by the Examiner for nonenablement is the lack of a specific teaching for extending graft survival by treatment of organ or cells at time periods other than prior to transplantation. The Federal Circuit advises that

> The specification need not contain an example if the invention is otherwise disclosed in a such manner that one skilled in the

> art will be able to practice it without an undue amount of experimentation.

See M.P.E.P. § 2164.02. Furthermore

> [T]he scope of enablement must only bear a reasonable correlation to the scope of enablement

See In re Fischer, 166 USPQ 18, 24 (CCPA 1970); see also M.P.E.P. § 2164.08. In this regard, Applicants invite the Examiner to review Exhibit A, U.S. Patent No. 5,756,492, which shows extension of graft survival by administering metalloprotoporphyrin to a *transplant recipient following organ implant*. A single dose of cobalt protoporphyrin administered subsequent to transplantation extended graft survival for periods similar to those observed for administration prior to transplant (Figure 2 and column 4, lines 61-67). In the present application, Applicants have provided evidence that metalloprotoporphyrins modulate heme oxygenase levels and that this modulation correlates with prolonging of graft survival (see Example 1). Following this premise, Applicants show that increasing heme-oxygenase levels directly by introducing and expressing a gene for heme oxygenase-I has a similar effect as treatment with cobalt protoporphyrin (Example 3). Given the teachings in the specification, a person skilled in the art could readily and reasonably extrapolate the observations with cobalt protoporphyrin to achieve similar results by delivering HO-1 gene into a target organ at time periods subsequent to transplantation.

As further support, a 37 C.F.R. § 1.132 declaration by co-inventor Dr. Suhasini Iyer is submitted herewith, together with supporting data, demonstrating that the administration of Ad HO-1 to the transplanted organ or to the organ recipient following transplantation is effective in extending graft survival.

In view of the foregoing, Applicants submit that the scope of the claims is commensurate with the scope of enablement when examined in reference to the content of the specification and the state of knowledge in the art. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-22, 26, and 27 stand rejected under 35 U.S.C. § 112, second paragraph as failing to particularly point out and distinctly claim the subject matter the Applicants regard as the invention. Applicants respectfully traverse.

The amendments have cancelled claims containing reference to "a nucleic acid that modulates heme-oxygenase-I activity." Since the rejections are rendered moot by the

amendments, Applicants respectfully request withdrawal of the rejection under 35 U.S.C § 112., second paragraph.

CONCLUSION

Applicants submit that all pending claims of the above referenced application are in compliance with all the requirements of patentability and are in condition for allowance. Accordingly, early notification of such allowance is earnestly solicited.

If after review, the Examiner feels there are further unresolved issues or determined that prosecution of the above reference application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY, LLP

Dated: 4/3/03

By: _____
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VERSION WITH MARKING TO SHOW CHANGES MADE

4. (Amended) The method according to Claim ~~2~~ 28, wherein said nucleic acid comprises nucleotides 81-944 of the human heme oxygenase-I nucleic acid sequence ~~shown in Figure 3 (SEQ ID NO: 1)~~ of SEQ ID NO: 1.

5. (Amended) The method according to Claim ~~1~~ 28, wherein said contacting is *ex vivo*.

6. (Amended) The method according to Claim ~~1~~ 28, wherein said contacting is *in vivo*.

7. (Amended) The method according to Claim ~~1~~ 28, wherein said organ transplant is an allograft.

9. (Amended) The method according to Claim ~~1~~ 28, wherein said contacting is with a liposome-mediated nucleic acid transfer vehicle.

10. (Amended) The method according to Claim ~~1~~ 28, wherein said contacting is with a viral-mediated nucleic acid transfer vehicle.

11. (Amended) The method according to Claim ~~1~~ 28, wherein said contacting is accomplished by direct injection of said nucleic acid into said organ.

12. (Amended) The method according to Claim ~~1~~ 28, wherein the heme oxygenase-I activity in said cells is increased.

16. (Amended) The method according to Claim ~~13~~ 29, wherein said contacting is *ex vivo*.

17. (Amended) The method according to Claim ~~13~~ 29, wherein said contacting is *in vivo*.

18. (Amended) The method according to Claim ~~13~~ 29, wherein said organ transplant is an allograft.

20. (Amended) The method according to Claim ~~13~~ 29, wherein said contacting is with a liposome-mediated nucleic acid transfer vehicle.

21. (Amended) The method according to Claim ~~13~~ 29, wherein said contacting is with a viral-mediated nucleic acid transfer vehicle.

22. (Amended) The method according to Claim ~~13~~ 29, wherein said contacting is accomplished by direct injection of said nucleic acid molecule into said organ.